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(54) Title: ACTIVATABLE SHEET FOR TOPICAL, THERAPEUTIC USE

(57) Abstract

A sheet comprises a biodegradable, non-thrombogenic, tissue-compatible material suitable for therapeutic use by topical administration, the sheet being flexible, hydratable and activatable so that it bonds to tissue, and retains its integrity on bonding.

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ACTIVATABLE SHEET FOR TOPICAL, THERAPEUTIC USE

Field of the Invention

This invention relates to a sheet-like dressing product or process, suitable for use in therapy, e.g. the treatment of wounds, surgical and non-surgical, and also the delivery of therapeutic agents.

Background of the Invention

Biocompatible adhesives are useful in various areas of therapy, e.g. in surgical procedures for repair or the creation of anastomosis. The use of biocompatible adhesive avoids suturing and stapling, and can provide immediate sealing of the treated tissue.

WO-A-9202238 discloses the use of biological adhesives, to bond separated tissues. The bonding or coating is enhanced by radiation, e.g. using a laser, to "cross-link" the adhesive to the tissue. WO-A-9622054 discloses further tissue adhesives, and in particular a fluid laser-activatable solder.

The effect of the radiant energy may be enhanced by incorporating a chromophore into the adhesive. Many such materials are known. They selectively absorb the energy, and convert that energy to heat which can be used to set the adhesive.

WO-A-9622797 describes the use of "colour change" chromophores. They and additives in the biological adhesive ensure that the colour changes only when the end point has been reached, thereby indicating to the user when sufficient energy has been applied, to induce cross-linking to the tissue. In addition, following the colour change, the chromophore will no longer absorb radiation. This means that excessive radiation will not give large temperature rises resulting in burning or other harmful effects. This is of importance during a variety of procedures.

The use of lasers, as indicated above, allows good control of the desired reaction, over small areas. However, for some applications, it is inconvenient to use laser-derived energy to induce tissue binding. For

example, a laser may not be available, or immediate medical attention may be required.

Tissue adhesives are typically applied to the desired locus as liquids, and then allowed to set, or activated. This provides limitations on their use. For example, a glue cannot always easily be applied during a procedure conducted *via* an endoscope. Further, not all desired additives, such as suitable temperature-sensitive dyes, may dissolve in the adhesive.

WO-A-9717025 discloses a cross-linked film of a non-collagenous protein such as bovine serum albumin, including glutaraldehyde. An argon beam was used to weld the film to tissue. Greater bond strength was obtained when the film was moist, having been (partially) dried under ambient conditions. Such a sheet may be brittle, and not malleable. Glutaraldehyde is not stabilised by bonds of a non-physiological nature, and is not a desirable component of material to be used in internal vessels.

WO-A-9214513 discloses a plasticised collagen sheet, for use in hernia repair. A patch that is intended for such use, i.e. as a reinforcing patch, is intended to remain in place, and should not be biodegradable. Further, collagen is thrombogenic, and therefore unsuitable for internal use.

Summary of the Invention

According to a first aspect of the present invention, a sheet suitable for use in therapy comprises a material suitable for therapeutic use by topical administration, the sheet being flexible, hydratable, activatable so that it bonds to tissue, and retains its integrity on bonding. Following the application of energy, the sheet becomes bonded to the tissue. This sheet may be applied to either external or internal surfaces, where it may act as a sealant, haemostat or dressing, or as a vehicle for drug delivery. It can be anti-fibrogenic, and non-scarring. The novel sheet does not suffer from the disadvantages, described above, of liquid tissue adhesives.

According to a second aspect of the present invention, a product suitable for use in therapy, in particular tissue repair, comprises a layer of a tissue-bonding or tissue-coating material and, superposed thereon, a separable or peelable layer of a thermogenic substance activatable to transmit heat to the tissue-bonding or tissue-coating material. If desired, the product may also comprise an indicator, e.g. as a layer through which heat can be transmitted to the material. Such a thermochrome may provide a visible indication of applied heat, and can therefore provide the user with an indication that (and also where) tissue binding has occurred.

The novel product that is the second aspect of the invention comprises the means to provide heat as an integral part thereof. If an indicator is present, it provides a means whereby the user, e.g. surgeon, first aider, medical practitioner or veterinary surgeon, can readily determine whether or not adequate heat has been provided in the desired area, so that the user can confidently remove the delaminatable part of the product, leaving only the set tissue-bonding or tissue-coating material *in situ*. A product of the invention without an indicator is suitable for use in circumstances where it is less important to know the extent of heating that has occurred, and where the user can have confidence in the means of generating heat, e.g. in the context of application over a predetermined period.

Description of the Invention

A sheet of the invention may comprise a single layer of the tissue-compatible material. Alternatively, especially where a thin layer is used and/or the material has insufficient integrity for the desired purpose, a carrier layer may be included. Suitable materials for the carrier layer are biocompatible. Examples are polybutyrate, polysaccharides, polytetrafluoroethylene and polyesters.

The sheet should have sufficient strength that it can hold together the apposing edges of a wound, or to seal a

surface, cavity or hole, or to be retained on the tissue until healing has been adequately achieved or until any therapeutic or biological agent incorporated in the sheet has been delivered for a sufficient time period. Appropriate parameters will be readily apparent to those skilled in the art.

The sheet can be used in contact with an external or internal body surface, and can be activated to bind the tissue, e.g. around a wound. A suitable tissue-compatible material will generally exhibit a degree of adhesion to tissue when first applied, so that it is not immediately displaced. Activation may cause the material itself to bond to tissue, or the sheet may include a coating of adhesive that is activatable. The tissue-compatible layer and any additional adhesive may be referred to herein as the tissue-bonding material.

The preferred tissue-compatible material for use in the present invention is a soluble protein, that is not part of the clotting cascade, such as albumin. Porcine albumin or porcine pericardeum or any other abundant non-thrombogenic protein, i.e. excluding collagen, may be used. For some procedures, genetically or chemically modified versions of these proteins may be used, for enhanced binding.

Flexibility (or malleability) is an important feature of a sheet according to this invention. This allows the sheet to be used in contact with small vessels that may be essentially cylindrical or have more complicated surfaces, e.g. of branching points. Such vessels include carotid artery, saphenous vein, splenic artery and others.

Flexibility is also important, where it is desired to deliver the product at a remote location, within the body, e.g. through an endoscope. For example, a sheet of the invention can be used for bowel anastomoses, or where it is necessary to seal an artery or vein after needle injection. For delivery to the prostate or other organs, the material may be delivered, through a delivery head, in a form that opens up to cover the surgical incision, where

it can be sealed in place. Local energy input might be achieved by providing a beam of white light.

In a further example, a non-thrombogenic angioplasty balloon, that is absorbed over time, may be provided by the invention. This is beneficial, since there will normally be thrombogenic tissue around the site. The seal may be achieved by heating with warm water.

In general terms, a sheet of the invention is an aid to anastomosis, whether vascular or of another type. The sheet effectively provides a tissue adhesive but, since it is not liquid, it will not enter arteries or the vascular system.

Another important feature of the invention is that the sheet should be biodegradable. The product will generally be used internally, to provide a tissue seal immediately after surgical intervention, and before natural tissue repair can occur. No permanent fixture is required or even desirable, in order for and therefore the present invention can provide a sealant comprising only biodegradable materials, primarily or solely proteinaceous, none of which is toxic. In particular, the use of low molecular weight compounds, such as glutaraldehyde, can be avoided.

The use of a material such as albumin, which is cysteine-rich, means that a sheet of the invention can be stabilised by the formation of S-S bonds. It is also a natural substrate for endogenous substances such as enzymes.

The tissue-compatible material should have sufficient plasticity that it can be moulded to a desired shape, or readily applied to the tissue at the site of treatment. Suitable plasticisers are biodegradable/non-toxic, and include fibrous proteins, carbohydrates such as sorbitol, glycerol and polyethylene glycol, as well as other sugars and alcohols, and other components which may reduce interactions between neighbouring polypeptides. Relatively low molecular weight plasticisers such as glycerol may be preferred. These or other additives may be adapted towards increasing the water-absorptive properties of the material

so that it can be presented as a gel or sol. The malleability of the sheet aids activation, and makes it particularly suitable for administration to a wet surface.

The amount of plasticiser to be used will be chosen having regard to the requirement for flexibility and the nature of the material to be plasticised. For example, a sorbitol concentration of 20 to 50% by mass of albumin is suitable for producing a flexible albumin sheet, and such amounts may also be suitable for other materials. The presence of plasticiser provides not only the desired flexibility but also hydratability. In particular, this means that a sheet of the invention adheres well to a wet surface, owing to osmotic pull. In certain circumstances, it may nevertheless be desirable to provide the sheet together with a liquid tissue adhesive.

In addition, the stability of the sheet, or the ability to activate it, may be enhanced by pretreatment, e.g. to partially set or cross-link (chemically or physically) the sheet. This is achieved, for example, by incubating the sheet at an elevated temperature, by exposing it to radiant energy, by treating it at an elevated pH, or by inclusion of additives such as cross-linking agents, before application of the sheet to the tissue. Pretreatment will generally be carrier out when the sheet is wet, if necessary after (re)hydration.

Pretreatment may make the sheet more robust, and easier to handle. It may also lead to lower energy levels, e.g. a lower temperature, being required to generate tissue-binding when the sheet is applied to biological material. This in turn may avoid the need to provide analgesia, and may make the sheet more suitable for use on sensitive tissue, e.g. the brain.

A sheet of the tissue-bonding material may be preformed to a suitable size, or cut to size for use *in situ*. The size of sheet will depend on the therapeutic application, however a typical sheet may be 40 mm long, 30 mm wide and 1.5 mm thick.

The tissue-compatible material may, or may not, contain a thermochromic compound (which undergoes a colour change on the application of heat) and/or a photochromic compound (which undergoes a colour change on the application of light). For example, the material may include a chromophore, such as methylene blue, which will change colour when the end point (when light-activated) has been reached; see also WO-A-9622797. The visual colour change may provide the user with an indication that sufficient energy has been applied to ensure tissue bonding has occurred. In addition, when the bonding reaction is complete, the resultant colour change ensures that the material will absorb no further radiant energy. This provides protection against excess energy input.

If a light-activated chromophore is present, it provides the user, e.g. a surgeon, first aider, medic or veterinary surgeon, with means to determine whether or not adequate energy has been provided in the desired area. The invention is also suitable for use without an indicator, e.g. in circumstances where it is less important to know the extent of radiation or heating that has occurred, and where the user can have confidence in the means of generating energy, e.g. in the context of application over a predetermined period.

According to this invention, a thermogenic substance may be provided as an integral part of a dressing. This substance may be activated, typically by the user. Examples of substances (including mixtures of substances) that can be used to generate heat will be evident to those skilled in the art.

For example, the thermogenic substance may comprise two components, typically a liquid and a powder, that undergo an exothermic reaction when mixed. A capsule or other sealed body may be provided, in which the two components are provided, in separate compartments. The compartments may be separated by a frangible membrane that can be broken by, say, the application of pressure, e.g. by crushing, bending, pulling or tearing. The exothermicity

of the reaction depends on the reactants, but can be sufficient to activate the tissue-bonding material without there being any danger of unnecessarily damaging tissue, e.g. at 35-70°C or higher.

Preferably, one of the reactants is water and the other is a solid that readily dissolves in water, exothermically. Many compounds exhibit exothermic enthalpies of solution, and this should generally be at least -50kJ.mol^{-1} at 298K. Examples of such compounds are LiI, KOH, $MgCl_2$, $MgBr_2$, MgI_2, $Mg(NO_3)_2$, $MgSO_4$, $CaCl_2$, $CaBr_2$, CaI_2, $AlCl_3$, $AlBr_3$, AlI_3 and $Al_2(SO_4)_3$. By way of example only, the limiting enthalpy of solution for $CaCl_2$ is -81.3 kJ mol^{-1}. Taking 40 g of $CaCl_2$, equivalent to 0.36 moles, and dissolving this in 0.1 L water will liberate 29300 J of heat. This energy heats a total mass of 140 g, and assuming the heat capacity to be that of pure water, i.e. 4 J K^{-1} g^{-1}, it can be calculated that the resulting temperature rise will be 52 K. Accordingly, amounts for appropriate compounds can be chosen with a view to the desired properties of a "heat pack" that is provided as an integral part of a dressing according to this invention.

As indicated above, a product of this invention may comprise a thermochrome or other indicator that there has been sufficient heating. This may be provided in the form of a thermochromic sheet. Such sheets are readily available, e.g. from Hallcrest and Fisher, and indicate that a particular temperature has been reached, e.g. by changing colour. Chromatic temperature indicators are also described in US-A-3633425, US-A-3951133, US-A-3830224, US-A-3765243 and US-A-3661142. They may provide reversible or non-reversible colour change. In addition, $CoCl_2$ and water (involving ligand exchange) or Evans blue and zinc formaldehyde sulphoxylate in water (by reduction of the azo dye) may be effective. Such materials may be provided as a separate sheet or as part of the thermogenic material.

If it is known that activation of the tissue-bonding material occurs at a given temperature, perhaps over a certain time, a dressing of the invention may include a

thermochromic sheet that indicates where a suitable therapeutic temperature is reached. When the indication is given, the user can be confident that adequate bonding has occurred, as well as providing the user with an indication as to where it has occurred. If provided as a separate sheet, the indicator can then be peeled off.

Layers of a dressing of this invention are generally separable, e.g. by peeling. The dressing will generally be provided in a form where the layers are initially at least joined together by some means, e.g. by a weak adhesive. It may also be appropriate to provide a release layer between separable layers of the novel dressing.

Depending on the presence of an indicator that provides a visible indication of heating, it may be desirable that any material containing the thermogenic substance is transparent. This, and the ability of the indicator material to conduct heat, will be particularly appropriate in the case where the thermogenic substance constitutes the top layer of the product, in use. Alternatively, the indicator layer is on top.

Further, the thermogenic material packaging should be transparent if the "heat-pack" includes an indicator within it. For example, Evans Blue is mixed with water and zinc formaldehyde sulphoxylate with powder that reacts with water exothermically. A colour change, from blue to a white precipitate, is observed once a desired temperature is reached. That temperature can be predetermined, according to the amounts of materials used.

As an alternative to heat, activation may comprise using a chemical activator such as a cross-linking agent, e.g. hexamethylenediisocyanate, and which may be applied by spraying or wetting. Alternatively, it may comprise using any suitable energy source, e.g. by applied heat or other irradiation. A suitable source of irradiation, when energy is applied from a non-integral source, is a laser. Irradiation may activate the tissue-bonding material without there being any danger of unnecessarily damaging tissue, e.g. to a temperature 35-70°C. In certain

applications, the temperature may be allowed to rise much higher for short periods, e.g. if a laser is used, without necessarily causing any harm.

Depending on the application, it may be appropriate to apply a high level of energy for a brief period. The local temperature may be high, but a thermochromic indicator will nevertheless provide a useful guide to protection of surrounding tissue. When activating with light, a "colour change" chromophore (see above) may be used. Preferred compounds of this type are methylene blue, or rose bengal in combination with a suitable reducing agent such as ascorbic acid.

If appropriate, layers of a dressing of this invention may be generally separable, e.g. by peeling. The dressing will generally be provided in a form where the layers are initially at least joined together by some means, e.g. by a weak adhesive. It may also be appropriate to provide a release layer between separable layers.

In another aspect of the present invention, a thermochromic material may be provided as part of the tissue-bonding layer, e.g. as a physical mixture. It may also be appropriate to provide a combination of thermogenic, thermochromic and tissue-bonding layers, with or without intervening release layers. In such a multilayer construction, an intermediate indicator sheet should of course allow heat to be transmitted to the tissue-bonding material.

A sheet or dressing of the present invention may be provided in any of various forms, e.g. as best suited to the intended use. It may be, for example, a dressing, haemostat or sealant. By way of example, it may be in the form of a conventional flat dressing, wrap, sealant or tube, open or with a closed end. A tube-like form, e.g. "chimney" shape, may be particularly suitable for application to certain anastomoses.

The sheet or dressing may include a therapeutic agent that is to be provided at a desired locus, e.g. a tumour.

It may thus serve as a vehicle for sustained, controlled release of a drug.

The invention will now be described by way of example only with reference to the accompanying drawing which is a cross-sectional view of a schematic representation of a product embodying this invention. The drawing shows a layer of a tissue-bonding or tissue-coating material 1, e.g. of albumin/sorbitol, a release layer 2, e.g. of PTFE, a "heat pack" 3, e.g. including a first compartment including powdered $CaCl_2$ having a frangible connection to a second compartment containing water, and a layer 4 of a material that changes colour when it has warmed to a temperature sufficient to set the tissue-bonding material, e.g. 35-70°C. In use, when placed on a wound, breaking the frangible connection allows the water and powder to react, and the heat of the exothermic reaction is transmitted to the tissue-bonding material 1, which is thus set. An adequate degree of heating is indicated by a change of colour in the layer 4. If desired, the layers 2, 3 and 4 can then be removed.

The following Examples illustrate the preparation of sheets of tissue-compatible material.

Example 1

0.9 g porcine albumin (Sigma) was dissolved in 2.5 ml water for injection (Phoenix Pharmaceuticals pH 7.7) and 0.5 ml of 1% w/v methylene blue for injection. To this solution, 0.585 g D-sorbitol was added and dissolved. Heating of this solution in a thermostatted water bath at 59°C increases the film rehydration time from 50 seconds (if left at room temperature) to 140 seconds. This solution was left to cool for 30 minutes and then cast on a level PTFE-coated surface. The film was left to dry at room temperature for 20 hours.

Example 2

0.9 g porcine albumin (Sigma) was dissolved in 4.5 ml of water for injection (Phoenix Pharmaceuticals, pH 7.7) and 0.5 ml of 1% w/v methylene blue for injection. To this solution, 0.5 glycerol was added and dissolved. This

solution was then cast on a level PTFE-coated surface. The film was left to dry at room temperature for 20 hours.

Example 3

0.9 g porcine albumin (Sigma) was dissolved in 0.5 ml water for injection (Phoenix Pharmaceuticals, pH 7.7) and 0.5 ml of 1% w/v methylene blue for injection. To this solution, 0.585 g D-sorbitol was added and dissolved. This solution is then heated at 61°C for 20 minutes to produce a sticky semi-jelly like solution and then left for 30 minutes to cool to room temperature. A silicone mandrel is then dipped in this solution producing an even coating of the albumin/sorbitol/methylene blue mixture stuck to the mandrel. The coated mandrel was partially dried using an air blower (without heat, i.e. at room temperature) and then left at room temperature for 20 hours to ensure the coating was completely dried. A tube-like product was obtained.

Example 4

0.9 g porcine albumin (Sigma) was dissolved in 5 ml water for injection (Phoenix Pharmaceuticals, pH 7.7). To this was added 0.5 ml glycerol and the whole mixed to give a homogeneous solution. The solution was cast on a level PTFE-coated surface and allowed to dry at room temperature for 20 hours. A film 5 cm square was cut from this material. 15 g $AlCl_3$ was placed in a thin-walled glass vessel within a sealed PVC bag of dimension 5 cm x 5 cm, containing 100 cm^3 of water. This bag was bonded to the plasticised albumin film using silicone based adhesive. Flexing or squeezing of the resulting package resulted in breaking of the glass vessel containing the $AlCl_3$, the resulting exothermic dissolution reaction giving a temperature rise of 80 K. When the package is applied, albumin film first, to a moist surface immediately following rupture of the $AlCl_3$-containing vessel, the heat generated is sufficient to achieve bonding between the film and the surface.

The compositions of Examples 1 to 3 all contain methylene blue and, as such, are capable of being light-

activated as well as thermally-activated. As examples, of a sheet which can only be thermally activated by either an integral or non-integral heat source, the methylene blue solution may be replaced by the equivalent amount of water for injection.

CLAIMS

1. A sheet comprising a biodegradable, non-thrombogenic, tissue-compatible material suitable for therapeutic use by topical administration, the sheet being flexible, hydratable and activatable so that it bonds to tissue, and retains its integrity on bonding.

2. A sheet according to claim 1, wherein the tissue-compatible material is a protein.

3. A sheet according to claim 1, wherein the tissue-compatible material is albumin.

4. A sheet according to any preceding claim, which comprises a light-activatable additive that provides a visible indication of activation.

5. A sheet according to any preceding claim, wherein the tissue-compatible material carries a coating of an activatable adhesive.

6. A sheet according to claim 5, wherein the coating extends around an area intended to contact the region of tissue to be treated.

7. A sheet according to any preceding claim, wherein the tissue-compatible material incorporates a plasticiser in an amount sufficient that the sheet remains attached to a wet surface on application thereto.

8. A sheet according to any preceding claim, wherein the tissue-compatible material is partially cross-linked or activated.

9. A sheet according to any preceding claim, which comprises a support layer.

10. A sheet according to any preceding claim, which additionally comprises a therapeutic agent.

11. A dressing which comprises separable layers of:

a sheet according to any preceding claim, which is heat-activatable; and

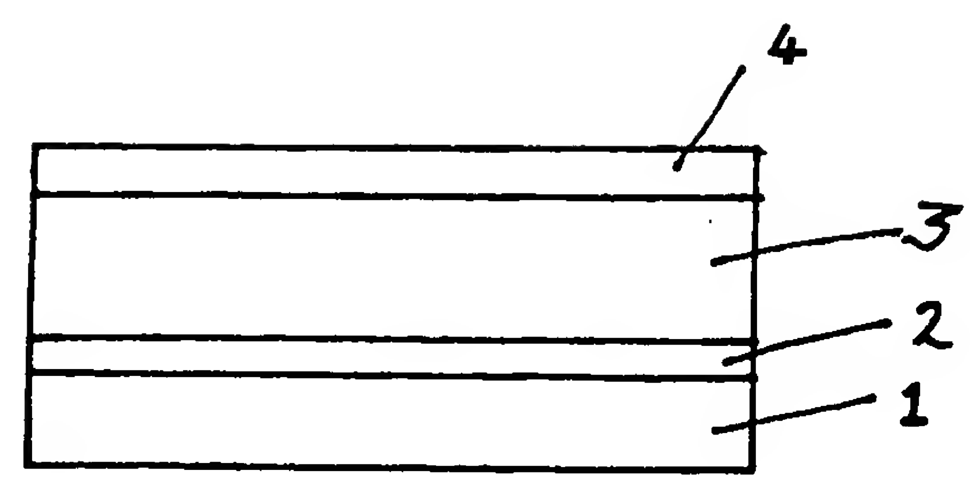
a thermogenic substance activatable to transmit heat to said material.

12. A dressing according to claim 11, which comprises also an indicator that provides a visible indication of heat applied to said material.

13. A dressing according to claim 12, wherein the indicator constitutes the top layer, in use.

14. A package comprising a sterile sheet or dressing according to any preceding claim.

15. A method for the treatment of tissue, which comprises applying thereto a sheet or dressing according to any of claims 1 to 13, and activating it so that it bonds to the tissue.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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/02717

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61L15/32 A61L24/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 17025 A (FUSION MEDICAL TECHNOLOGIES IN ;WALLACE DONALD G (US); REICH CARY) 15 May 1997 (1997-05-15) page 9, line 21 -page 11, line 10 claims 1,5-7,21,25-27	1-3, 5-10,14, 15
X	WO 92 14513 A (INTERFACE BIOMEDICAL LAB CORP) 3 September 1992 (1992-09-03) page 16, paragraph 2 - paragraph 4 page 7, line 35 -page 9, line 6	1,2,4-8, 10-15
X	WO 96 22054 A (DAWES JUDITH MARGARET ;TRICKETT RODNEY IAN (AU); LAUTO ANTONIO (AU) 25 July 1996 (1996-07-25) page 7, line 33 -page 9, line 20 page 14, line 17 -page 15, line 12	1-8, 10-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

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